



Ophthalmic Anti-Inflammatories Therapeutic Class Review (TCR)

May 4, 2016

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May 2016

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Corticosteroids		
dexamethasone (Maxidex®) ¹	Alcon	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe ▪ Corneal injury
dexamethasone sodium phosphate ²	generic	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe ▪ Corneal injury
difluprednate (Durezol®) ³	Alcon	<ul style="list-style-type: none"> ▪ Treatment of inflammation and pain associated with ocular surgery ▪ Treatment of endogenous anterior uveitis
fluorometholone (FML®) ⁴	generic, Allergan	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
fluorometholone (FML Forte®) ⁵	Allergan	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
fluorometholone (FML S.O.P.®) ⁶	Allergan	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
fluorometholone acetate (Flarex®) ⁷	Alcon	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
loteprednol gel, ointment (Lotemax®) ^{8,9}	Bausch & Lomb	<ul style="list-style-type: none"> ▪ Treatment of post-operative inflammation and pain following ocular surgery
loteprednol suspension (Lotemax®) ¹⁰	Bausch & Lomb	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe ▪ Treatment of post-operative inflammation following ocular surgery
prednisolone acetate (Omnipred®, Pred Forte®) ^{11,12}	generic; Alcon, Allergan	<ul style="list-style-type: none"> ▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe ▪ Treatment of corneal injury (Omnipred)
prednisolone acetate (Pred Mild®) ¹³	Allergan	<ul style="list-style-type: none"> ▪ Treatment of mild to moderate noninfectious allergic and inflammatory disorders of the lid, conjunctiva, cornea, and sclera (including chemical and thermal burns)
prednisolone sodium phosphate ¹⁴	generic	<ul style="list-style-type: none"> ▪ Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe ▪ Corneal injury
rimexolone (Vexol®) ¹⁵	Alcon	<ul style="list-style-type: none"> ▪ Treatment of anterior uveitis ▪ Treatment of post-operative inflammation after ocular surgery

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Corticosteroids – Intravitreal		
dexamethasone (Ozurdex®) ¹⁶	Allergan	<ul style="list-style-type: none"> Treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) Treatment of non-infectious uveitis affecting the posterior segment of the eye Treatment of diabetic macular edema
fluocinolone (Iluvien®) ¹⁷	Alimera	<ul style="list-style-type: none"> Treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure
fluocinolone (Retisert®) ¹⁸	Bausch & Lomb	<ul style="list-style-type: none"> Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye
triamcinolone acetonide (Triesence®) ¹⁹	Alcon	<ul style="list-style-type: none"> Treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids Visualization during vitrectomy
NSAIDs		
bromfenac (Prolensa™, BromSite™) ^{20,21,22}	generic, Bausch & Lomb, Sun	<ul style="list-style-type: none"> Treatment of post-operative inflammation and reduction of ocular pain secondary to cataract extraction/surgery
diclofenac ²³	generic	<ul style="list-style-type: none"> Treatment of post-operative inflammation secondary to cataract extraction Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery
flurbiprofen (Ocufen®) ²⁴	generic, Allergan	<ul style="list-style-type: none"> Inhibition of intraoperative miosis
ketorolac (Acular LS®) ²⁵	generic, Allergan	<ul style="list-style-type: none"> Reduction of ocular pain, burning, and stinging after corneal refractive surgery
ketorolac (Acuvail®) ²⁶	Allergan	<ul style="list-style-type: none"> Treatment of pain and inflammation following cataract surgery
nepafenac (Ilevro™, Nevanac®) ^{27,28}	Alcon	<ul style="list-style-type: none"> Treatment of pain and inflammation associated with cataract surgery

Ketorolac (Acular®) is indicated for treatment of post-operative inflammation secondary to cataract extraction and temporary relief from ocular itching related to seasonal allergic conjunctivitis.²⁹

OVERVIEW

Uveitis is an inflammation of the middle layer of the eye or uvea, consisting of the iris, ciliary body and choroid.^{30,31} Uveitis may be caused by eye trauma, secondary to autoimmune diseases or infection, or may be idiopathic in nature.³² It may present as acute, chronic, or recurrent attacks, with unilateral pain or photophobia.³³ Aqueous cells and flare, due to cellular infiltration and protein exudation into the anterior chamber, are seen as spots and haze on slit-beam examination; both are signs of ocular inflammation. If left untreated, uveitis can lead to glaucoma, cataract, or retinal edema and ultimately loss of vision. Initial treatment for uveitis typically includes ophthalmic corticosteroids (topical drops or intravitreal implant) to reduce pain and inflammation.

Temporal arteritis, affecting the superficial temporal arteries, is a systemic inflammatory vasculitis of unknown etiology that occurs in older individuals and can result in systemic, neurologic, and ophthalmologic complications.³⁴ Permanent visual impairment is estimated in up to 20% of patients with the condition. Timely initiation of therapy may prevent irreversible damage, including blindness. The mainstay of therapy includes corticosteroids which are typically for up to 2 years in duration.

To ensure its transparency, the cornea is maintained in a dehydrated state by the pumping action of the endothelial cells controlled by Na⁺/K⁺-ATPase.³⁵ Damage to the corneal endothelium may result in increased corneal thickness and ultimately corneal decompensation and loss of vision. Ophthalmic surgery, such as cataract extraction, generally results in moderate damage to the endothelium and a transient increase in corneal thickness. Endothelial cell count (density) and corneal thickness measurements are used to assess the degree of endothelial damage.

Ophthalmic anti-inflammatories, including corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), are used to treat inflammatory conditions of the eye, including those due to trauma and surgery.

Topical corticosteroids are available in drops, gels, and ointments and are the standard of care for treating ophthalmic inflammation. Ophthalmic corticosteroids can, however, lead to side effects, such as increased intraocular pressure, cataract development, and increased risk of ocular infection.

Ophthalmic NSAIDs are primarily used during and after ophthalmic surgery.³⁶ These agents reduce inflammation in the cornea and conjunctiva and help maintain papillary dilatation during surgery. Ophthalmic NSAIDs also control inflammation during surgery and in the first few days following surgery. Treatment with ophthalmic NSAIDs is not associated with the undesirable side effects as the ophthalmic corticosteroids as listed above. The American Academy of Ophthalmology (AAO) reports that postoperative topical regimens following cataract surgery vary among practitioners.³⁷ There are no controlled studies establishing optimal regimens for the use of various topical agents, including topical corticosteroids and NSAIDs, following cataract surgery.

Corticosteroids that are administered via intravitreal injection and implantation are FDA approved to treat inflammatory conditions of the eye that are not related to injury or surgery, such as uveitis and macular edema. Diabetic macular edema (DME) is a microvascular complication of diabetes and is a leading cause of visual impairment and blindness in diabetic patients.³⁸ DME is a progression of diabetic retinopathy and is caused by leakage of dilated capillaries and microaneurysms in the macular area.³⁹ Intravitreal corticosteroids are administered by a licensed healthcare professional under aseptic conditions. As with the topically-applied ophthalmic products, intravitreal agents are associated with side effects including, cataract formation and elevated intraocular pressure. Injection-related side effects include retinal detachment, vitreous hemorrhage, bacterial endophthalmitis, and sterile endophthalmitis.

PHARMACOLOGY^{40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65}

Topical corticosteroids exert an anti-inflammatory action. Aspects of the inflammatory process, such as edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, deposition of collagen, scar formation, and fibroblastic proliferation, are suppressed. Topical corticosteroids are effective in acute inflammatory conditions of the conjunctiva, sclera, cornea, lids, iris, and anterior segment of the globe, as well as in ocular allergic conditions. In ocular disease, route of administration depends on the site and extent of the condition being treated.

Ophthalmic NSAIDs have analgesic and anti-inflammatory activity. The mechanism of action is thought to be through the inhibition of cyclooxygenase enzymes, which are essential in prostaglandin production. Prostaglandins disrupt the blood-aqueous humor barrier, produce vasodilation, and increase vascular permeability, leukocytosis, and intraocular pressure (IOP).

Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. These agents inhibit the miosis induced during the course of cataract surgery and have no significant effect on IOP.

During vitrectomy, dispersal of the water-insoluble triamcinolone acetonide (Triesence) particles within the vitreous chamber provides contrast to the transparent vitreous humor and membranes.

PHARMACOKINETICS^{66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91}

Highly potent corticosteroids include dexamethasone acetate, difluprednate, prednisolone acetate, and prednisolone phosphate; moderate potency steroids are rimexolone, dexamethasone phosphate, and fluorometholone acetate.^{92,93} The efficacy of a topical corticosteroid is based on potency, vehicle, drug concentration, duration of action, contact time, and ocular penetration. Most topically-applied corticosteroids penetrate the eye via the cornea. In general, acetate and alcohol forms are more lipophilic and lead to longer contact time and better penetration due to the lipid nature of the cornea, while the phosphate form is more hydrophilic and leads to decreased corneal penetration.⁹⁴ In addition, presence of intraocular inflammation may result in increased absorption.

The duration of effect of dexamethasone intravitreal implant (Ozurdex) lasts approximately 1 to 3 months. The fluocinolone acetonide intravitreal implants are designed to deliver drug over approximately 30 months (Retisert) and 36 months (Iluvien).

Intravitreal administration allows a corticosteroid dose to be delivered over prolonged period of time delivery and allows the dose to bypass the blood–retinal barrier.⁹⁵

Due to the topical nature of this drug class, systemic absorption for most products is below detectable levels. Ketorolac (Acular, Acular LS, Acuvail) does achieve measurable systemic levels, but there is no clinical impact.^{96,97,98} Nepafenac (Ilevro, Nevanac) is a prodrug that is metabolized via ocular tissue hydrolases to the active NSAID, amfenac.⁹⁹ Low systemic levels of nepafenac and amfenac have been observed after topical administration to the eye. Nepafenac has been shown to penetrate the cornea more rapidly and provides more complete (80% versus 50%) and longer lasting inhibition of prostaglandin synthesis (greater than 6 hours versus 3 hours) and vascular permeability (8 hours versus 4 hours) than diclofenac.^{100,101} After topical instillation, systemic levels of bromfenac (generic, Prolensa, BromSite) and diclofenac remain below the level of detection.^{102,103}

CONTRAINDICATIONS/WARNINGS^{104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,,126,127,128,129,130}

Ophthalmic corticosteroids, including dexamethasone (Ozurdex) and fluocinonide (Iluvien, Retisert) intravitreal implants, are contraindicated in patients with viral (epithelial herpes simplex keratitis, vaccinia, varicella), mycobacterial, or fungal infections of the eye. The label for triamcinolone intravitreal suspension (Triesence) contains warnings for the use of corticosteroids in general and the risk of infection due to fungi or viruses; it should be used with caution in patients with ocular herpes

simplex and should not be used in those with active infection. Triamcinolone (Triesence) is contraindicated in patients with systemic fungal infections.

Dexamethasone intravitreal implant (Ozurdex) and fluocinonide implant (Iluvien) are contraindicated in patients with glaucoma who have cup to disc ratios of greater than 0.8. Dexamethasone intravitreal implant is also contraindicated in patients with a rupture of the posterior lens capsule.

Prolonged use of ophthalmic corticosteroids, including intravitreal agents, may cause ocular hypertension and/or glaucoma, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, and secondary ocular infections. Perforations have occurred in patients with thinning of the cornea or sclera.

The products in this review are contraindicated in patients with known hypersensitivity to any component of the product. Bromfenac (Prolensa) contains sodium sulfite which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, particularly in those with asthma. As with all NSAIDs, cross-hypersensitivity in patients with aspirin and other NSAID-hypersensitivities is possible; caution should be used in such patients. There have been reports of bronchospasm or exacerbation of asthma associated with the use of ketorolac tromethamine ophthalmic solution in patients who either have a known hypersensitivity to aspirin/NSAID or a past medical history of asthma.

Surgical complications have been associated with intravitreal products. Intravitreally administered corticosteroid implants and suspensions have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Following implantation of fluocinolone (Iluvien, Retisert), patients may experience an immediate and temporary decrease in visual acuity lasting 1 to 4 weeks post-operatively. Intravitreal implants may migrate to the anterior chamber if the posterior lens capsule is not intact; the fluocinolone implant (Retisert) has been associated with separation of implant components.

Refractive stability of patients undergoing corneal refractive procedures and treatment with diclofenac usage has not been well established. There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues when used in this setting; therefore, patients should be monitored for a year following use in this setting. Use with caution in patients at increased risk of bleeding.

In March 2016, the Food and Drug Administration (FDA) warned the public that eye drop bottles that have loose plastic safety seals or tamper-evident rings (also known as a collar or band) below the bottle cap may cause eye injuries during administration if the seal/ring falls onto the eye.¹³¹ All affected products will require a change in the packaging design.

Precautions

NSAIDs may cause keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation.¹³² These events may be sight-threatening. Patients with evidence of corneal epithelial breakdown should discontinue use of topical NSAIDs immediately and should be closely monitored. Patients who might be at risk for complications include those with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time. Using ophthalmic NSAIDs beyond the 14 days may increase a patient's risk of severe corneal adverse events.

Topical NSAIDs and topical corticosteroids may slow or delay healing and concomitant use of topical NSAIDs and topical steroids may increase this risk.

Bromfenac (generic, Prolensa, **BromSite**), ketorolac (Acular, Acular LS, Acuvail) and nepafenac (Ilevro, Nevanac) should not be administered while wearing contact lenses. Except for the use of a bandage hydrogel soft contact lens during the first 3 days following refractive surgery, diclofenac 0.1% solution should not be used by patients currently wearing soft contact lenses.

Precautions for triamcinolone intravitreal suspension include elevated blood pressure, salt and water retention, hypokalemia, gastrointestinal perforation, behavioral and mood disturbances, decreased bone density, and weight gain.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

DRUG INTERACTIONS^{133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150, 151, 152, 153,154,155,156,157,158}

Due to the topical nature of these anti-inflammatory agents, drug interaction studies have not been systematically performed. Nepafenac (Nevanac) has been investigated for potential impact on the cytochrome P450 system; no potential impact was identified.

When ophthalmic medications need to be used concurrently, they should be administered at least 5 minutes apart.

ADVERSE EFFECTS

Drug	Transient burning/stinging	Ocular irritation	Corneal edema	Vision change
Corticosteroids				
dexamethasone (Maxidex) ¹⁵⁹	nr	nr	nr	reported
dexamethasone sodium phosphate ¹⁶⁰	reported	reported	nr	reported
difluprednate (Durezol) ¹⁶¹	nr	1-5	2-5	1-5
fluorometholone (FML) ¹⁶²	reported	reported	nr	reported
fluorometholone (FML Forte) ¹⁶³	reported	reported	nr	reported
fluorometholone (FML S.O.P.) ¹⁶⁴	nr	reported	nr	nr
fluorometholone acetate (Flarex) ¹⁶⁵	nr	nr	nr	reported
loteprednol gel (Lotemax) ¹⁶⁶	nr	nr	nr	nr
loteprednol ointment (Lotemax) ¹⁶⁷	nr	nr	4-5	nr
loteprednol suspension (Lotemax) ¹⁶⁸	5-15	< 5	< 5	5-15
prednisolone acetate (Omnipred, Pred Forte) ^{169,170}	nr	reported	nr	nr
prednisolone acetate (Pred Mild) ¹⁷¹	nr	nr	nr	reported
prednisolone sodium phosphate ¹⁷²	nr	nr	nr	reported
rimexolone (Vexol) ¹⁷³	1-5	1-5	< 1	1-5
Corticosteroids - Intravitreal				
dexamethasone (Ozurdex) ¹⁷⁴	nr	7	nr	nr
fluocinolone (Iluvien) ¹⁷⁵	nr	8	4	5-29
fluocinolone (Retisert) ¹⁷⁶	nr	10-40	50-90	10-40
triamcinolone acetonide (Triesence) ¹⁷⁷	nr	< 2	nr	< 2

Adverse Effects (continued)

Drug	Transient burning/stinging	Ocular irritation	Corneal edema	Vision change
NSAIDs				
bromfenac 0.07% (Prolensa) ¹⁷⁸	nr	nr	nr	3-8
bromfenac 0.075% (BromSite) ¹⁷⁹	nr	1-8	nr	nr
bromfenac 0.09% ¹⁸⁰	2-7	2-7	nr	nr
diclofenac ¹⁸¹	15	< 5	< 5	< 5
flurbiprofen (Ocufen) ¹⁸²	reported	reported	nr	nr
ketorolac (Acular LS) ¹⁸³	20-40	1-10	1-10	nr
ketorolac (Acuvail) ¹⁸⁴	nr	1-6	1-6	1-6
nepafenac (Ilevro, Nevanac) ^{185,186}	reported	1-5	1-5	5-10

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. nr = not reported.

The most common ocular adverse event reported in clinical studies for loteprednol ointment was anterior chamber inflammation at a rate of approximately 25%. In studies with loteprednol gel, this was reported in 5% of subjects.¹⁸⁷

Benzalkonium chloride is a preservative used in many ophthalmic preparations; however it can cause a dose- and duration-dependent breakdown of the corneal epithelium and increased absorption. The following products contain benzalkonium chloride: bromfenac (BromSite), dexamethasone (Maxidex), dexamethasone sodium phosphate, fluorometholone (FML, FML Forte), fluorometholone acetate (Flarex), loteprednol (Lotemax suspension, gel), ketorolac (Acular, Acular LS), nepafenac (Ilevro, Nevanac), prednisolone (Omnipred), prednisolone acetate (Pred Mild), prednisolone sodium phosphate, and rimexolone (Vexol).^{188,189,190} Flurbiprofen (Ocufen) contains thimerosal, which can cause allergic contact conjunctivitis.^{191,192} Sorbic acid, which may cause less damage and irritation to the ocular surface, is the preservative in difluprednate (Durezol).¹⁹³ Fluorometholone (FML S.O.P.) uses phenylmercuric acetate; ocular side effects are rare, but mercurialentis (deposition of pigment on the lens) has been reported.¹⁹⁴ Ketorolac (Acuvail) does not contain any preservative.

The most common adverse reactions following use of bromfenac 0.07% (Prolensa), reported in 3% to 8% of patients, include anterior chamber inflammation, foreign body sensation, eye pain, and photophobia.¹⁹⁵ The most common adverse reactions following use of bromfenac 0.075% (BromSite), reported in 1% to 8% of patients, include anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.¹⁹⁶

The most common adverse effects reported with fluocinonide intravitreal implant (Iluvien) are cataracts (82%) and myodesopsia (floaters; 21%). With fluocinonide intravitreal implant (Retisert) and triamcinolone suspension (Triesence) the most common adverse effects are cataracts and increased

ocular pressure; and with dexamethasone implant (Ozurdex) are increased ocular pressure (25%) and conjunctival hemorrhage (22%).

Results from clinical studies indicate that ophthalmic NSAIDs have no significant effect on intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery. In clinical studies with diclofenac, elevated intraocular pressure following cataract surgery was reported in approximately 15% of patients undergoing cataract surgery. Studies reported increased ocular pressure following cataract surgery in 5 to 10% of patients treated with nepafenac 0.1% suspension (Nevanac).¹⁹⁷

SPECIAL POPULATIONS^{198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214, 215, 216,217,218,219,220,221,222,223,224}

Pediatrics

In a 3-month, double-masked trial, a similar safety profile was observed for difluprednate (Durezol) and prednisolone acetate ophthalmic suspension 1%, in 79 pediatric patients, 0 to 3 years of age, in the treatment of inflammation following cataract surgery.²²⁵

Safety and efficacy of fluocinolone (Iluvien) and dexamethasone (Ozurdex) implants have not been established in pediatric patients, while safety and effectiveness of fluocinolone intravitreal implant (Retisert) have not been established in patients younger than 12 years. The labeling for triamcinolone intravitreal suspension (Triesence) states that safety and efficacy of corticosteroids is similar in pediatric and adult populations.

Fluorometholone (FML, FML Forte, FML S.O.P.) has been studied in children ages 2 years and older.²²⁶ The safety and efficacy of other corticosteroid products in this class have not been studied, but dexamethasone drops and prednisolone are reportedly safe in children, in general.²²⁷

Safety and effectiveness in pediatric patients have not been established in children for bromfenac (generic, Prolensa, **BromSite**), diclofenac, flurbiprofen sodium (Ocufen), ketorolac tromethamine 0.45% solution (Acuvail), and loteprednol (Lotemax gel, ointment, suspension).^{228,229,230,231,232,233} Nepafenac (Ilevro, Nevanac) has not been studied in children less than 10 years of age.²³⁴ Ketorolac products (Acular, Acular LS) have been approved for use in children age 3 years and older.^{235,236}

rimexolone (Vexol) versus fluorometholone

In 54 children who underwent surgery for bilateral symmetric strabismus, rimexolone and fluorometholone were compared for anti-inflammatory efficacy and ocular hypertension.²³⁷ One eye was randomized to receive rimexolone 1% and the other eye received fluorometholone 0.1%; both medications were administered 4 times daily for 4 weeks. IOP increased significantly in both treatment groups, but the mean peak IOP was significantly higher with rimexolone than fluorometholone (19.7 mm Hg versus 17.6 mm Hg, respectively; $p < 0.001$). More children in the rimexolone group had no conjunctival erythema on days 13 and 20 ($p = 0.03$). Authors concluded that IOP should be monitored in children receiving rimexolone therapy on a regular basis.

Pregnancy

With the exception of triamcinolone (Triesence), which is Pregnancy Category D, agents in this class assigned a Pregnancy Category are Pregnancy Category C. Due to the known effects of NSAIDs and the

prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system, including the closure of ductus arteriosus, the use of many of these ophthalmic NSAIDs during late pregnancy should be avoided. Bromfenac (BromSite) has not been assigned a Pregnancy Category based on the Pregnancy and Lactation Labeling Rule (PLLR). There are no adequate and well-controlled studies of bromfenac 0.075% in pregnant women to inform any drug associated risks; its risks are expected to be similar to other ocular NSAIDs with minimal systemic absorption, as described above.

DOSAGES

Drug	Dosage	Availability
Corticosteroids		
dexamethasone 0.1% suspension (Maxidex) ²³⁸	Apply 1 to 2 drops to the conjunctival sac of the affected eye(s) every 4 to 6 hours; in severe disease, may administer drops hourly, tapering to discontinuation as the inflammation subsides	5 mL
dexamethasone sodium phosphate 0.1% solution ²³⁹	Apply 1 to 2 drops to the conjunctival sac of the affected eye(s) every hour during the day and every 2 hours at night; reduce frequency to every 4 hours once a favorable response occurs	5 mL
difluprednate 0.05% emulsion (Durezol) ²⁴⁰	<u>Inflammation and pain with ocular surgery:</u> Apply 1 drop to the conjunctival sac of the affected eye(s) 4 times daily beginning 24 hours after surgery and continuing for 2 weeks post-op, then twice daily for another week, then taper based on response <u>Endogenous anterior uveitis:</u> Apply 1 drop to the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering, as clinically indicated	5 mL
fluorometholone 0.1% suspension (FML) ²⁴¹	Apply 1 drop to the conjunctival sac of the affected eye(s) 2 to 4 times daily (may be used every 4 hours during initial 24 to 48 hours)	5, 10, 15 mL
fluorometholone 0.25% solution (FML Forte) ²⁴²	Apply 1 drop to the conjunctival sac of the affected eye(s) 2 to 4 times daily (may be used every 4 hours during initial 24 to 48 hours)	5, 10 mL
fluorometholone 0.1% ointment (FML S.O.P.) ²⁴³	Apply half-inch ribbon to the conjunctival sac of the affected eye(s) 1 to 3 times daily (may be used every 4 hours during initial 24 to 48 hours)	3.5 g tube
fluorometholone acetate 0.1% solution (Flarex) ²⁴⁴	Apply 1 to 2 drops to the conjunctival sac of the affected eye(s) 4 times daily (may be used as 2 drops every 2 hours during initial 24 to 48 hours)	5 mL
loteprednol 0.5% gel (Lotemax) ²⁴⁵	Apply 1 to 2 drops into the conjunctival sac of the affected eye(s) 4 times daily starting 24 hours after surgery for 2 weeks	5 g
loteprednol 0.5% ointment (Lotemax) ²⁴⁶	Apply half-inch ribbon into the conjunctival sac of the affected eye(s) 4 times daily starting 24 hours after surgery for 2 weeks	3.5 g tube
loteprednol 0.5% suspension (Lotemax) ²⁴⁷	<u>Anti-inflammatory:</u> Apply 1 to 2 drops 4 times daily (up to every hour during the first week, if necessary) <u>Cataract surgery:</u> Apply 1 to 2 drops 4 times a day starting 24 hours after surgery for 2 weeks	5, 10, 15 mL
prednisolone acetate 1% solution (Omnipred, Pred Forte) ^{248, 249}	<u>Omnipred:</u> Apply 2 drops to the affected eye(s) 4 times daily <u>Pred Forte:</u> Apply 1 to 2 drops into the conjunctival sac of the affected eye(s) 2 to 4 times daily (may increase dosing frequency during the initial 24 to 48 hours if needed)	1, 5, 10, 15 mL
prednisolone acetate 0.12% solution (Pred Mild) ²⁵⁰	Apply 1 to 2 drops to the conjunctival sac of the affected eye(s) 2 to 4 times daily (may increase dosing frequency during the initial 24 to 48 hours if needed)	5, 10 mL
prednisolone sodium phosphate 1% solution ²⁵¹	Apply 1 to 2 drops to the conjunctival sac of the affected eye(s) every hour during the day and every 2 hours at night; reduce frequency once a favorable response occurs	5, 10, 15 mL
rimexolone 1% solution (Vexol) ²⁵²	<u>Anterior uveitis:</u> Apply 1 to 2 drops every hour (while awake) for 1 week, then every 2 hours for the second week, then taper off until resolved <u>Ocular surgery:</u> Apply 2 drops 4 times a day starting 24 hours after surgery for a duration of 2 weeks	5, 10 mL

Dosages (continued)

Drug	Dosage	Availability
Corticosteroids - Intravitreal		
dexamethasone (Ozurdex) ²⁵³	Implanted intravitreally by healthcare provider	0.7 mg implant
fluocinolone (Iluvien) ²⁵⁴	Surgically implanted inferior to the optic disc and posterior to the equator of the eye; designed to release drug over 36 months	0.19 mg implant
fluocinolone (Retisert) ²⁵⁵	Surgically implanted into posterior segment of the affected eye(s); designed to release drug over 30 months	0.59 mg implant
triamcinolone acetonide (Triesence) ²⁵⁶	<u>Inflammation:</u> 4 mg intravitreally <u>Visualization:</u> 1 to 4 mg intravitreally	40 mg/1 mL vial
NSAIDs		
bromfenac 0.07% solution (Prolensa) ²⁵⁷	Apply 1 drop once daily to affected eye(s) starting 1 day prior to surgery, continued on the day of surgery and through the first 14 days post-op	3 mL
bromfenac 0.075% solution (BromSite) ²⁵⁸	Apply 1 drop to affected eye (s) twice daily starting 1 day prior to surgery, continued on the day of surgery and through the first 14 days post-op	5 mL
bromfenac 0.09% solution ²⁵⁹	Apply 1 drop to affected eye(s) twice daily starting 24 hours post-op for 2 weeks	1.7 mL, 2.5 mL
diclofenac 0.1% solution ²⁶⁰	<u>Cataract surgery:</u> Apply 1 drop to affected eye(s) 4 times daily starting 24 hours post-op for 2 weeks <u>Refractive surgery:</u> Apply 1 to 2 drops within 1 hour prior to surgery, then 1 to 2 drops 15 minutes post-op, then 1 to 2 drops 4 times a day for up to 3 days	2.5, 5 mL
flurbiprofen sodium 0.03% solution (Ocufen) ²⁶¹	Beginning 2 hours before surgery, instill 1 drop to affected eye(s) every 30 minutes for a total of 4 drops	2.5 mL
ketorolac tromethamine 0.4% solution (Acular LS) ²⁶²	Apply 1 drop to affected eye(s) 4 times a day for up to 4 days as needed for burning or stinging following refractive surgery	5 mL
ketorolac tromethamine 0.45% solution (Acuvail) ²⁶³	Apply 1 drop to affected eye(s) twice daily beginning 1 day prior to surgery and continuing through the first 2 weeks post-op	0.4 mL single-use vials
nepafenac 0.3% suspension (Ilevro) ²⁶⁴	Apply 1 drop to affected eye(s) once daily beginning 1 day prior to surgery; continue on the day of surgery, and through the first 2 weeks post-op; Administer an additional drop 30 to 120 minutes prior to surgery	1.7, 3 mL
nepafenac 0.1% suspension (Nevanac) ²⁶⁵	Apply 1 drop to affected eye(s) 3 times daily beginning 1 day prior to surgery; continue on the day of surgery, and through the first 2 weeks post-op	3 mL

CLINICAL TRIALS

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the ophthalmic use of all drugs in this class. Randomized controlled comparative trials for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Several studies were performed in the perioperative setting which is not applicable to the outpatient utilization. These studies were excluded from this review.

There are no published comparative trials of intravitreal corticosteroids.

Topical Corticosteroids

difluprednate 0.05% (Durezol) versus prednisolone acetate 1%

In a multicenter, randomized, contralateral-eye, double-masked trial, the effects of difluprednate 0.05% and prednisolone acetate 1% on corneal thickness and visual acuity after cataract surgery were compared on 52 patients (104 eyes) that underwent bilateral phacoemulsification.²⁶⁶ For each patient, the first eye randomly received difluprednate 0.05% or prednisolone acetate 1%; the other eye received the alternative. Before surgery, 7 doses were administered over 2 hours; 3 additional doses were given after surgery, before discharge. For the remainder of the day, corticosteroids were administered every 2 hours, then 4 times daily during Week-1, and twice daily during Week-2. On Day-1 after surgery, corneal thickness was 33 μm less in difluprednate-treated eyes ($p=0.026$), uncorrected and best corrected visual acuity were significantly better with difluprednate than prednisolone by 0.093 logMAR lines ($p=0.041$) and 0.134 logMAR lines ($p<0.001$), respectively. Endothelial cell density was 195.52 cells/ mm^2 higher in difluprednate-treated eyes at day 30 ($p<0.001$). Retinal thickness at Day-15 was 7.74 μm less in difluprednate-treated eyes ($p=0.011$).

loteprednol suspension (Lotemax) versus prednisolone acetate

In 2 studies of acute anterior uveitis, loteprednol 0.5% suspension was compared to prednisolone acetate 1% for reduction in ocular signs and symptoms. Both studies were parallel, randomized, double-blind, active controlled comparisons.²⁶⁷ In the first study, treatment was administered 8 times daily and lasted for 42 days in 70 patients. The second study was 28 days in duration with initial treatment given 16 times daily in 175 patients. At the end of the first trial, 74% of loteprednol patients and 88% of prednisolone patients achieved resolution. The difference was not significant. In the second study, the 2 groups were not different with resolution rates of 72% for loteprednol and 87% for prednisolone groups. Elevated intraocular pressure (IOP) was observed more frequently in the prednisolone group. This difference in resolution rates between loteprednol and prednisolone acetate

appears in the prescribing information for loteprednol. The use of a more potent corticosteroid than loteprednol, such as prednisolone acetate 1%, is suggested for the treatment of anterior uveitis.²⁶⁸

rimexolone (Vexol) versus prednisolone acetate

Rimexolone 1% suspension and prednisolone acetate 1% were compared in 48 patients undergoing cataract extraction with phacoemulsification followed by posterior chamber intraocular lens implantation in a randomized, double-blind trial.²⁶⁹ Both therapies were administered 4 times daily for 15 days. Patients were examined on Days-1, -3, -7, and -15. Efficacy was similar in both groups as defined by anterior chamber cells, anterior chamber flare, and conjunctival hyperemia. IOP measurements were similar in both groups.

Two multicenter studies compared the efficacy and safety of rimexolone 1% suspension and prednisolone acetate 1% in patients with uveitis.²⁷⁰ Administration of each drug was every 2 hours initially with a gradual taper over 4 weeks. No significant differences in response rates were found between the 2 groups at the various evaluation periods or at the end of treatment. Prednisolone patients were found to have a higher likelihood of IOP elevation in both studies.

A randomized, triple-blinded, parallel comparison was completed evaluating rimexolone 1% and prednisolone 1% in 78 patients with acute, chronic, or recurrent anterior uveitis.²⁷¹ Patients instilled 1 or 2 drops of the assigned drug hourly while awake for the first week, then every 2 hours during the second week, then 4 times daily in the third week, then following a taper to complete 4 weeks of therapy. Anterior chamber cells and flare reactions were monitored periodically during the study. Overall clinical efficacy was similar between the 2 treatments. The IOP was also similar during the study; however, 3 patients receiving rimexolone 1% and one patient receiving prednisolone 1% had elevated IOP during the study.

Topical NSAIDs

diclofenac versus flurbiprofen (Ocufen)

In a double-blind trial, 43 patients undergoing cataract extraction were randomized to diclofenac sodium 0.1% or flurbiprofen 0.03%.²⁷² The assigned medication was instilled every 6 hours for 3 doses prior to surgery, then 4 drops over 90 minutes just prior to surgery. After surgery, patients administered the assigned medication 4 times daily for 3 to 6 weeks. Patients were examined 1, 3, and 6 weeks post-operatively. There were no statistically significant differences between the treatment groups for conjunctival hyperemia, corneal surface changes, IOP, or anterior chamber inflammation.

diclofenac versus ketorolac (Acular)

In a double-masked, randomized trial during the post-operative period of cataract extraction and implantation of an intraocular lens, a total of 120 patients were treated with either diclofenac 0.1% solution or ketorolac tromethamine 0.5% solution 4 times daily for 30 days.²⁷³ Treatment began the first post-operative day after surgery. Objective measurements of inflammation and toxicity were made at 3 post-operative visits. The anti-inflammatory effects were similar at all 3 post-operative visits. Both treatments were equally tolerated.

In a long-term follow-up to the above study, the primary endpoint was to evaluate the incidence of post-operative posterior opacification.²⁷⁴ Patients were followed for 3 years and received yttrium-aluminum-garnet (YAG) laser capsulotomies and were evaluated for any existing post-operative

posterior opacification. The incidence of post-operative posterior opacification and YAG capsulotomies were similar (12% in each treatment group). Adverse effects from therapy were also similar in both groups.

In a double-blind, randomized study, diclofenac 0.1% solution and ketorolac 0.5% solution were compared in 30 patients for efficacy in relieving corneal pain after refractive surgery.²⁷⁵ Patients underwent radial keratotomy and were monitored for post-operative pain and instillation comfort. Both diclofenac and ketorolac were similarly effective in reducing ocular pain and had similar comfort on instillation ($p=0.29$).

ketorolac 0.5% (Acular) versus ketorolac 0.4% (Acular LS)

The 2 formulations of ketorolac tromethamine 0.4% and 0.5% ophthalmic solutions were compared for effectiveness and patient tolerance in 40 patients undergoing phacoemulsification and lens implantation.²⁷⁶ In a double-masked study, patients were randomized to receive 1 of the 2 strengths of ketorolac starting 15 minutes prior to surgery. After surgery, patients administered 1 drop 4 times daily for 1 week, then twice daily for 3 weeks. Patients were examined on Day-1, -7, and -30. On Day-1, more patients reported foreign body sensation or stinging and burning in the ketorolac 0.5% group (70%) than the ketorolac 0.4% group (40%; $p<0.05$). There were no significant differences between the 2 groups for best-corrected visual acuity, IOP, slit-lamp assessment of cells, or cell/flare measured using the laser cell/flare meter.

ketorolac (Acular) versus loteprednol suspension (Lotemax)

In a randomized, double-blind trial looking at controlling inflammation after cataract surgery, 60 patients were randomized to receive ketorolac tromethamine 0.5% or loteprednol etabonate 0.5% suspension 4 times a day starting 24 hours after surgery.²⁷⁷ There was no statistically significant difference in any measurement of post-operative inflammation between the 2 groups measured by external slit-lamp examination on post-operative days 1, 4, 7, and 30.

ketorolac (Acular LS) versus nepafenac (Nevanac)

A randomized study compared the efficacy of ketorolac tromethamine 0.4% and nepafenac 0.1% eye drops for prophylaxis of cystoid macular edema (CME) after small-incision cataract extraction.²⁷⁸ The incidence and severity of CME were evaluated by retinal foveal thickness on optical coherence tomography (OCT) after 1, 4 and 12 weeks in patients who were randomized to ketorolac tromethamine 0.4%, nepafenac 0.1%, or placebo. One hundred and twenty-six eyes of 126 patients were included and evaluated. The between-group differences in visual outcomes, central corneal thickness and endothelial cell density, or measurements performed by spectral-domain OCT were not statistically significant.

ketorolac (Acular) versus prednisolone acetate

In a double-blind trial, 59 patients requiring cataract extraction were randomized to receive either ketorolac tromethamine 0.5% solution or prednisolone acetate 1%.²⁷⁹ Treatment was administered according to the following schedule: 1 to 2 drops 4 times daily for 1 week; 3 times daily for the second week; 2 times daily for the third week; and once daily for the fourth week. At day 28, both treatments produced comparable reductions in intraocular inflammation and pain after cataract surgery and were well tolerated by patients. No adverse events were reported.

ketorolac (Acular) versus rimexolone (Vexol)

Ketorolac tromethamine 0.5% and rimexolone 1% were compared in 2 small studies evaluating the control of inflammation following cataract surgery in 36 patients.²⁸⁰ Patients were randomized to either agent in a double-blind manner, and the assigned drops were administered 4 times daily starting 24 hours post-operatively. No difference was found between the 2 agents for the post-operative inflammation at any time period. No difference was noted in the IOP between the groups.

nepafenac 0.3% (Ilevro) versus nepafenac 0.1% (Nevanac) versus placebo

In 2 double-masked, randomized clinical trials, nepafenac ophthalmic suspension 0.3% and 0.1% were compared to vehicle dosed daily starting 1 day prior to cataract surgery, continued on the day of surgery, and for the first 2 weeks postoperatively.²⁸¹ Nepafenac suspension showed better clinical efficacy compared to its vehicle. In the first study, inflammation resolved at postoperative day 14 in 65% of nepafenac ophthalmic suspension 0.3% patients (n=851), in 32% of vehicle patients (n=211), and in 67% of nepafenac ophthalmic suspension 0.1% patients (n=845) (95% CI, 33% [26-40]) for nepafenac ophthalmic suspension 0.3% and vehicle). Ocular pain at day 14 resolved in 86% of nepafenac 0.3% patients, 46% of placebo patients, and 87% of nepafenac 0.1% patients (95% CI 40% [32-47]) for nepafenac ophthalmic suspension 0.3% and vehicle. In the second study, nepafenac 0.3% (n=540) resolved inflammation (postoperative day 14) versus vehicle (n=268) in 61 and 24% of patients, respectively. Ocular pain resolved in 84 and 38% of nepafenac 0.3% and vehicle groups, respectively.

SUMMARY

Ophthalmic corticosteroids have long been used as first-line therapy for the treatment of ophthalmic inflammatory conditions prior to the increased use of ophthalmic NSAIDs. The ophthalmic NSAIDs offer equivalent anti-inflammatory efficacy for post-operative inflammation. Ophthalmic corticosteroids have the potential for long-term adverse events, such as increased intraocular pressure (IOP), cataract formation and increased risk of ocular infection, but studies comparing ophthalmic corticosteroids to ophthalmic NSAIDs have not shown clinical differences in adverse event profiles when treatment duration is 30 days or less. There are no data to suggest a significant advantage for any one product in either subclass in terms of clinical effectiveness or adverse effect profile, nor are there data that show a difference between agents in different subclasses.

Products with invasive intravitreal administration (Iluvien, Retisert, Triesence, Ozurdex) are available and injected by a licensed healthcare professional. These agents (Ozurdex, Retisert, Triesence) are approved to treat uveitis, typically when topical therapy fails. In addition, dexamethasone (Ozurdex), and fluocinolone (Iluvien) implants are indicated to treat diabetic macular edema, dexamethasone implant is also indicated to treat macular edema following branch/central retinal vein occlusion.

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